

Case Reports

# KIF1C Variants Are Associated with Hypomyelination, Ataxia, Tremor, and Dystonia in Fraternal Twins

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## Abstract

**Background:** *KIF1C* (Kinesin Family Member 1C) variants have been associated with hereditary spastic paraplegia and spastic ataxia.

**Case report:** We report fraternal twins presenting with cerebellar ataxia and dystonic tremor. Their brain MRI showed a hypomyelinating leukoencephalopathy. Whole exome sequencing identified a homozygous *KIF1C* variant in both patients.

**Discussion:** *KIF1C* variants can manifest as a complex movement disorder with cerebellar ataxia and dystonic tremor. *KIF1C* variants may also cause a hypomyelinating leukoencephalopathy.

**Keywords:** KIF1C, dystonic tremor, cerebellar ataxia, hypomyelinating leukoencephalopathy

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## Introduction

*KIF1C* (Kinesin Family Member 1C MIM 603060) variants have been associated with hereditary spastic paraplegia (HSP) and spastic ataxia-2 (SPAX2 MIM 611302).<sup>1-4</sup> Patients bearing *KIF1C* variants were first reported in two consanguineous Palestinian and Moroccan families with early-onset cerebellar ataxia followed by pyramidal symptoms,<sup>1</sup> at a locus previously associated with autosomal recessive spastic ataxia-2 (SPAX2 MIM 611302).<sup>5</sup> Subsequently, Novarino et al. identified a homozygous deletion of exon 14–18 in the original SPAX2 family, confirming that *KIF1C* was the SPAX2 gene.<sup>2</sup> The disease was then designated as spastic paraplegia type 58 (SPG58).<sup>3</sup>

Thanks to whole exome sequencing (WES), the phenotype of genes known to be associated with HSP keeps expanding and the overlap between HSPs and other neurological diseases suggests common cellular mechanisms.<sup>6</sup> Hereinafter, we report two fraternal twins carrying a homozygous *KIF1C* variant detected by WES and presenting with cerebellar ataxia, dystonic tremor, and a hypomyelinating leukoencephalopathy.

## Case description

Seventeen-year-old fraternal twins (a female and a male) of Moroccan descent were referred to a neurometabolic reference center for early-onset cerebellar ataxia associated with white matter abnormalities on brain MRI.

Their asymptomatic parents were first cousins, and medical family history was unremarkable. Pregnancy, delivery (at 37 gestational weeks), and early development were normal for both patients. They started walking at around 1 year of age, but frequent falls occurred during infancy, complicated by writing difficulties and dysarthria at primary school. Gait and speech worsened during adolescence, but both patients obtained their bachelor's degree. At 17-year-old, the boy presented with cerebellar ataxia with a SARA (Scale for the Assessment and Rating of Ataxia) score of 12/40, associated with dystonic tremor. He displayed increased deep tendon reflexes in the lower extremities and a right Babinski sign. Vibration sense was mildly reduced in the lower extremities. Oculomotor examination showed a saccadic pursuit with dysmetric saccades and a bilateral ptosis. The girl displayed a similar phenotype with cerebellar ataxia – SARA score of 10/40 – associated with a dystonic tremor predominantly in the neck, which appeared at 12-year-old. Vibration sense was reduced in the lower extremities but without any pyramidal sign. Oculomotor examination showed a saccadic pursuit with dysmetric saccades. Over 3 years of observation, cerebellar ataxia remained stable in both patients, but dystonic tremor became more prominent in the upper limbs and executive functions declined. A formal neuropsychological evaluation with WAIS-IV scale was performed at 19-year-old. Both patients showed heterogeneous scores. The boy obtained a verbal comprehension index (VCI) of 84, a perceptual organization index (POI) of 72, a working memory index (WMI) of 68, and a processing speed index (PSI) of 55. The girl obtained a VCI of 83, a POI of 84, a WMI of 80, and a PSI of 66. Furthermore, the boy presented with increasing spasticity in the lower limbs and the girl had an episode of intestinal occlusion (later diagnosed as Crohn's disease) that worsened her tremor and dystonic features. Patients' neurological examination is shown at 20-year-old (Video 1).

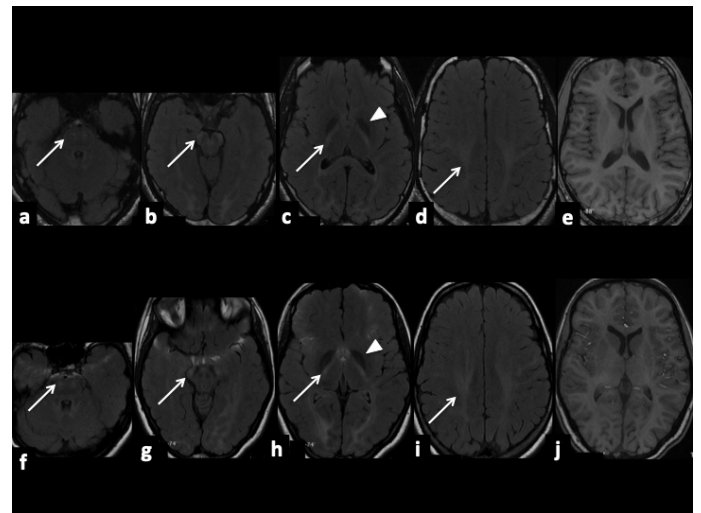


**Video 1. Clinical examination in both fraternal twins.** They both present with cerebellar gait and dysmetria as well as distal postural and action tremor of the upper limbs. In addition, the boy displays mild spastic gait and the girl dystonic tremor of the neck (barely noticeable on the video due to regular botulinum toxin injections) as well as dystonic postures of the upper limbs.

Polymyographic recording found postural and action tremor of the upper limbs in both twins and dystonic tremor of the neck in the girl (frequency of 5.5 Hz), without myoclonus. Brain MRI showed diffuse but mild T2- and FLAIR-hyperintensities, with T1-isointensity, of the internal capsules, optic radiations and cortico-spinal tracts, associated with mild T2-hypointensities of the globus pallidi, suggesting a hypomyelinating leukoencephalopathy (Figure 1).<sup>7</sup> DaTscan and nerve conduction studies were normal. Visual, brainstem auditory, somatosensory, and motor evoked potentials displayed diffuse conduction anomalies, compatible with a hypomyelinating disorder. So far, the demyelinating neuropathy has remained asymptomatic with normal visual campimetry, visual acuity, and optical coherence tomography in both patients. A targeted panel of 45 genes associated with leukodystrophies and leukoencephalopathies was performed, but failed to reveal the cause of the disease. The probands and their unaffected parents consented to WES. A homozygous variant in *KIF1C* (NM\_006612.5:c.1019+1dup) was detected in both twins and confirmed by Sanger sequencing. Both parents were heterozygous carriers of the variant. The c.1019+1dup variant (class 5, pathogenic) occurs at one of the splicing donor sites and alters the splice site recognition, is not present in the Exome Variant Server (EVS), in the Exome Aggregation Consortium (ExAC) nor in GnomAD databases.

## Discussion

Our patients show that biallelic *KIF1C* variants can cause a predominant movement disorder characterized by cerebellar ataxia and dystonic tremor. Brain MRI may provide additional diagnostic clues in the presence of a hypomyelinating leukoencephalopathy.



**Figure 1. Brain MRI of fraternal twins (boy: a-b-c-d-e and girl: f-g-h-i-j).** Axial FLAIR-weighted images (a-b-c-d/f-g-h-i) showing diffuse but mild hyperintensities (arrows) of the cortico-spinal tracts with T1-isointensity (e and j), associated with mild hypointensities of the globus pallidi (arrowheads), suggesting a hypomyelinating leukoencephalopathy.

*KIF1C* variants have been associated mostly with complicated forms of HSP, initially called SPAX2<sup>5</sup> and then HSP58.<sup>3</sup> Cerebellar ataxia may occur in infancy, later complicated by spastic paraplegia.<sup>4</sup> Adult-onset forms of spastic ataxia have also been reported.<sup>3</sup> Of note, heterozygous mutation carriers may present with a mild phenotype such as demyelinating sensory-motor neuropathy or mild spasticity.<sup>3</sup> This intriguing mode of inheritance, with a severe phenotype in recessive forms and a milder one in heterozygous carriers, has been previously described for other forms of HSP, such as SPG7.<sup>8</sup> Dystonia has been previously reported in three patients<sup>1,3,4</sup> (two at the cervical level and one affecting upper extremities), otherwise presenting with a complicated HSP phenotype. As observed in other recessive ataxias (i.e., ataxia-telangiectasia variants or ataxia with vitamin E deficiency), our patients exhibited a predominant movement disorder. This observation is in line with recent research highlighting a putative role of the cerebellum in the pathophysiology of dystonia.<sup>9</sup> White matter abnormalities of the cortico-spinal tracts have been observed by several groups in young adults with *KIF1C* variants.<sup>1,3,4</sup> However, these studies did not specify the T1 appearance of patients' FLAIR and T2 hyperintense lesions, which would help discriminating between demyelinating and hypomyelinating lesions.<sup>7</sup> Here, we provide clear evidence for a pattern of hypomyelinating leukoencephalopathy in our *KIF1C*-mutated patients, consistent with the common onset of the disease in infancy.

*KIF1C* (Kinesin Family Member 1C MIM 603060) encodes a microtubule-based motor protein belonging to the kinesin family.<sup>10</sup> Two other members of this family (*KIF5A* and *KIF1A*) have been associated with pure and complicated forms of HSP, SPG10, and SPG30, respectively.<sup>11,12</sup> *KIF1C* is localized at the pericentrosome and was initially thought to participate in protein transport from the Golgi to the endoplasmic reticulum.<sup>13</sup>

More recently, the putative role of *KIF1C* on the structure of the Golgi complex<sup>14</sup> and in membrane dynamics in podosome turnover<sup>15–17</sup> have been demonstrated. Several model systems have been proposed to explore the role of *KIF1C* in neuronal development. *KIF1C* knock-out mice did not show any neurological phenotype, presumably because of the redundant expression of other kinesins in brain.<sup>18</sup> Instead, a *KIF1C*-mutated cattle has been proposed as the first efficient animal model to explore *KIF1C* function.<sup>19</sup> *KIF1C*-deficient cattle display a progressive form of ataxia named ataxia of Charolais, mimicking spastic ataxia in humans. Authors hypothesized that *KIF1C* loss of function alters membrane trafficking and membrane wrapping in oligodendrocytes along axons, highlighting the role of *KIF1C* protein in preserving the structural integrity and function of myelin.<sup>19</sup> The observation of a hypomyelinating leukoencephalopathy in our patients, supporting the early involvement of oligodendrocytes in the disease process, is of particular relevance in this context.

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